REMARKS:

In the Office Action dated June 27, 2006, claims 1-14, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-14 remain in this application.

Claims 1-7 and 12-14 were rejected under 35 USC §103(a) as unpatentable over Neidhardt (WO 93/16099) in view of Ron (U.S. Patent No. 5,171,579) and Avis. Applicants understanding is that Neidhardt is cited for the disclosure of MP52. Ron is cited for the disclosure of adding mannitol to pharmaceutical formulations containing BMPs as a cryogenic protector and Avis is cited for the disclosure of optimizing lyophilization formulations, specifically adding mannitol so that the freeze dried plug occupies the same volume as the original solution. The problem which the present invention solves was to provide bone morphogenetic factor human MP52 as a lyophilized product while avoiding the drawback of volume reduction (shrink) occurring during storage and also to avoid cohesion of MP52 at the time of reconstitution. "Shrinkage" refers to the decrease in volume during lyophilization. The lyophilized preparation still possesses a residual water content which decreases during storage so that the total volume is reduced. "Cohesion" means that the lyophilized product takes longer to reconstitute. In addition, part of the product does not dissolve at all and is present in the form of an aggregate. Such aggregates are undesirable because they do not have the same activity as the dissolved protein. Applicants respectfully point out that none of the cited references address shrinkage and cohesion problems when MP52 is lyophilized.

The Avis reference provides a general discussion of lyophilization but has nothing to do with proteins in particular. Many substances are indicated as being possible agents to make the dried-product plug occupy essentially the same volume as

that of the original solution. According to Avis, numerous substances are preferably used as a combination and mannitol is only one of the many possible substances. The disclosure of Avis would not have guided one skilled in the art to select mannitol for use with MP52 from the numerous recited substances. As noted in the present application and in the previously submitted declaration signed by Hideki Ichikawa, Applicants have found that products used in the prior art were not successful when used with MP52 and thus the use of specific substances is not predictable from the general disclosure in the cited prior art.

Ron does not cure the deficiencies in Avis as Ron does not suggest that mannitol is suitable for the use in a lyophilized product of MP52 either. Ron is not directed to the lyophilization of proteins but discloses a composition comprising an osteogenic protein and a porous particulate polymer matrix. Ron mainly deals with the porous particulate polymer matrix for providing in situ scaffolding for the osteogenic protein. Providing the osteogenic protein in a lyophilized form in the described composition is mentioned as one possible variant. Ron suggests that additional optional components such as cryogenic protectors might be useful and mannitol is indicated to protect from degradation during lyophilization. However, this disclosure is part of the general description and no examples were carried out in order to show that mannitol is in fact suitable in the connection with osteogenic proteins. The suggestion of mannitol as a possible cryogenic protector does not show that mannitol is in fact successful and it was unpredictable from Ron whether or not the use of mannitol would be helpful in context with a lyophilized MP52 product.

Ron is directed to osteogenic products in general and particularly the BMP-family. Though MP52 and BMP-2 belong to the same protein family, applicants point out that they do not exhibit identical physical behavior. Properties such as solubility cannot be transferred from one protein to another since individual amino acids on the protein surface have different hydrophobicity and can also show different solution behavior and different tendencies to aggregation. In general, it is not possible to transfer data from one protein to another even if they are in the same family. In order to illustrate the different physical properties of these two proteins, applicants point out Patent Application WO 93/00050 by Ron. Example 3, especially Table 4, shows that BMP-2 has a good solubility in basic amino acids, e.g. in 500 mm lysine x ≥ 0.9 mg/ml. In contrast to this, MP52 according to the present invention, when used with lysine (0.25-25% with 1 mg/ml of MP52, page 2 of the description), has bad solubility after lyophilization resulting in cohesion/formation of aggregate.

Applicants respectfully contend that one skilled in the art could not have predicted that mannitol could be combined with bone morphogenetic factor human MP52 to produce a lyophilized product which avoids the drawback of volume reduction (shrink) occurring during storage and also avoids cohesion of MP52 at the time of reconstitution. Since not all cryoprotectants can be used with all proteins, applicants contend that one skilled in the art would not reasonably expect mannitol to be useful with MP52 without testing. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 7-14 were rejected under 35 USC §103(a) as unpatentable over Neidhardt in view of Ron and Avis further in view of Chang. Chang was cited for the

disclosure of surface active agents to protect proteins from freeze and surface induced denaturation. Applicants contend that Chang also shows that no general predictions can be made about the lyophilization conditions for specific proteins. Chang, on page 1325, first column, discloses that "despite the numerous freeze-thawing studies on proteins, the choice of these solutes and development of stable formulations is still largely emperical because of the lack of a full understanding of the relative importance of the various stresses arising during freezing and of mechanisms by which additives protect proteins against these stresses". In other words, for every protein, optimum conditions must be determined individually and cannot be predicted from the results obtained with other proteins.

Applicants also point out that Ron states that mannitol can be used to protect BMP proteins from degradation during lyophilization. However, MP52, is stable without mannitol. During storage of lyophilized MP52 no obvious degradations occur and there is no formation of chemical degradation products as compared to the storage of MP52 with mannitol. Thus, one would not combine Neidhart with Ron to prevent degradation of MP52 since MP52 does not form chemical degradation products. Mannitol is primarily used for the prevention of cohesion as well as for achieving a low water content in the present invention. Avis and Chang do not cure the deficiencies in Ron and Neidhardt as neither of these references suggest that general predictions can be made about the lyophilization conditions for specific proteins.

Applicants respectfully point out that the argumentation in the office action with regard to the mixing ratios used is inapplicable. The Office Action argues on pages 4 and 5 that Avis indicates that mannitol can be used as a solution of 5-25%, i.e. 50

mg/ml to 250 mg/mi. In view of Ron, the Office Action further assumes that 2-4 mg/ml of a BMP would be used (column 2, lines 22-28). The starting point that 2-4 mg/ml of BMP is used for lyophilization, however, is not correct. The concentration indicated in Ron, refers to the final product, i.e. the lyophilized product after solution (including reconstitution from a lyophilized form), before it is used in patients. When using BMPs in patients, it is important that BMPs are dissolved in high concentrations (2-4 mg/ml) so that the volume used is not too high. Before lyophilization, the volume is not as important since the solvent is removed, only the weight ratio from protein to mannitol is important. Therefore, the indication of a concentration of 2-4 mg/ml should not be considered as the calculation before lyophilization as suggested in the office action. Patent Application WO 93/00050 by Ron indicates in Example 4 that BMP-2 together with mannitol and epsilon-carboxylic acid is directly lyophilized on the matrix. 22 mg of BMP-2 and 8 mg of mannitol are used, i.e. a mixing ratio of 1:364. The skilled artisan would have assumed that BMPs are used with considerably higher dosages of mannitol than is the case according to the present invention with MP52 wherein the optimum mixing ratio from 1:5-50 is sufficient. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 7-10 and 12-14 were rejected under 35 USC §103(a) as unpatentable over Neidhardt , Ron and Avis in view of Chang, further in view of Hansen, in light of the MeSH definition of "poloxamer". As discussed above, the combination of Neidhardt, Ron, Avis and Chang, does not suggest that mannitol should be used when lyophilizing MP52 in view of the fact that during storage of lyophilized MP52 no obvious degradations occur and there is no formation of chemical degradation products.

Hansen is cited only for the disclosure of surfactants for stabilization of freeze-dried proteins and does not cure the deficiencies in Neidhardt, Ron, Avis and Chang regarding the use of mannitol with MP52 in a lyophilized composition. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 8 and 9 were rejected under 35 USC §112, second paragraph, as indefinite. The term "substance" has been deleted from claims 8 and 9. In view of these amendments applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 1-14 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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